

OTS: 60-11,545

JPRS: 2564

9 May 1960

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- USSR -

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19980108 159

THE PATHOGENESIS OF DIABETES MELLITUS*

[This is a translation of an article written by Prof. S. G. Genes (Khar'kov) in Kazanskiy Meditsinskiy Zhurnal (Kazan' Medical Journal), Vol 40, No 6, 1959, pages 8-14.]

Our ideas of the pathogenesis of diabetes mellitus have changed considerably during the past 40 years. Our current concepts result from the acquisition of new data on the role of the central nervous and endocrine systems in the pathogenesis of diabetes mellitus; new data on the metabolic processes taking place in it; and, finally, the elicitation of processes in the picture of this disease which attest to the injury to the organism in the absence of insulin, and the reactions which characterize its control of the inflicted injury.

While 40 years ago it was considered universally accepted that diabetes mellitus develops basically as the result of pancreatic insufficiency, it is impossible at the present time to visualize the pathogenesis of diabetes mellitus without taking into account also the role of other endocrine glands especially that of the anterior hypophyseal lobe, the suprarenal glands, cerebral cortex, and hypothalamus.

1

It was demonstrated* in this laboratory that diabetic hyperglycemia is less pronounced during the state of sodium amytal narcosis, while the insulin hypoglycemia is corrected much more slowly. What, then, causes the inhibition in both instances?

Diabetic hyperglycemia develops as the result of an increased secretion of sugar into the blood by the liver (2). The mechanism of correction of insulin hypoglycemia is similar. The increased influx of glucose into the blood from the liver is caused by the enhanced glycogenolysis and gluconeogenesis. Both phenomena are caused by the effect of stimulated sympathetic nerves on the liver and by the increased secretion of hormones of the adrenal medullar and of glucocorticoids from the adrenal. The sympathetic nerves are stimulated by impulses from the hypothalamus and, in turn, enhance the secretion of the hormones of the adrenal medullary: adrenalin and noradrenalin. The glucocorticoids are secreted in an increased

* Reported at the Second Povolzh'ye Conference of Therapeutists in Saratov, 18 June 1959.

quantity under the influences of increased adrenocorticotrophic hormone from the anterior hypophyseal lobe. The latter is also stimulated by hypothalamic impulses.

Thus, when insulin is absent or excessive, conditions are created which effect an activation of the mechanism of glycolysis and gluconeogenesis.

But how is the hypothalamus itself stimulated under these conditions? The hypothalamic functions, as is known, are to a great extent dependent on the cortex of the large hemispheres. The cortex regulates, coordinates, and controls them. When the cortex is impaired, many functions of the hypothalamus become disorganized. When insulin is absent or excessive, conditions are created which are bound to contribute to the depression of the cerebral cortex and, accordingly, to the disorganization of the hypothalamic functions. The following data which we have obtained support this hypothesis.

We showed in experiments conducted jointly with N. S. Veller and P. M. Charnaya (5) that the absence or excess of insulin leads to a decreased extraction of blood sugar by the cerebrum.

Since blood glucose is practically the sole source of energy for the cerebrum, especially for its cortex, the absence or excess of insulin leads to cerebral carbohydrate starvation. Inasmuch as the transfer of oxygen to the cerebrum is basically associated with the extraction of glucose, it is natural that with the diminution of the extraction of glucose the transfer of blood oxygen into the brain is also decreased. As a result, the brain becomes deficient in oxygen as well as carbohydrate. This deficiency especially leads to the depression of the cerebral cortex of the large hemispheres, since the cortex functions with a considerably larger utilization of the glucose oxidation energy, at the expense of the subcortical formations. This situation, in turn, disorganizes the above-described metabolic functions of the hypothalamus and, as a result, a diabetic hyperglycemia develops and the insulin hypoglycemia is corrected.

The above data enable us to explain why a deep sodium amytal narcosis inhibits the development of diabetic hyperglycemia and the elimination of insulin hypoglycemia. Sodium amytal causes a narcotic state which affects not only the cortex but also depresses the hypothalamic functions, at least the metabolic ones. In this respect its action differs from that of ether and chloroform, the latter presumably having a lesser effect on the hypothalamus. Their different effect on the metabolic hypothalamic functions is supported by the fact that the blood sugar level remains normal during a 25-hour sodium amytal narcosis, while it is rapidly increased under the effect of ether and chloroform.

In weakening the hypothalamic metabolic functions, sodium amytal has -- as do other narcotics -- a slight effect on other

links of the mechanism responsible for the increase of glycogenolysis and gluconeogenesis. For example, the liver continues to react to adrenalin and glucocorticoids: the adrenal medulla, to the impulses coming from the sympathetic nerves; and the adrenal cortex to ACTH. The adrenocorticotrophic function of the anterior hypophyseal lobe responds to hypothalamic impulses in ether and chloroform narcosis, as well as to other stresses.

Thus, in the absence of insulin, the cerebral cortex becomes depressed and thus leads to stimulation of the hypothalamus, as well as of the mechanism of glycogenolysis and gluconeogenesis. However, depression of the cerebral cortex which follows inhibition of the hypothalamus is accompanied by a considerably weaker reaction of gluconeogenesis.

2

The primary result of the termination of insulin action is a marked decrease in the transfer of blood sugar into the tissues, which leads to a markedly diminished utilization. Upon the decrease of oxidation of glucose (reaction of dehydrogenation) There is reduction of the quantity of hydrogen needed for the hydrogenation of pyridinenucleotide. Therefore, at the expense of the reduced form of pyridinenucleotide there is an increase in the quantity of its oxidized form. Decrease of the reduced CoA in diabetes mellitus leads to lower synthesis of fatty acids, to the decrease of the hydrogenated form of glutathione, and to a negative nitrogen balance. The scarcity of hydrogen for hydrogenation in diabetes mellitus diminishes the formation of high energy phosphorus compounds which are the accumulators and carriers of a large quantity of energy.

In diabetes mellitus there is a decrease of transformation of carbohydrates in the Dickens-Khorek cycle (6, 7, 8), and a diminution of activity of the glucose-6-phosphatase and 6-phosphogluconate dehydrase. The content of ribonucleic acid is correspondingly decreased. The Dickens-Khorek cycle is particularly expressed in the liver, adrenal glands, and the crystalline lens. Therefore the possibility is not excluded that its decrease bears some relationship to the not-infrequently encountered impairment of the functions of these organs in diabetes mellitus. The diminished carbohydrate oxidation in the suprarenals leads to a decrease of the reduced form of triphosphopyridinecucleotide and to the augmentation of its oxidized form (TPN) which contributes to the increased formation of 11-oxysteroids of the cortisone type in the adrenals. These, as is known, play a large part in the new formation of glucose from non-carbohydrates (9).

In skeletal muscles and the central nervous system the energy of the glucose is utilized within the Embden-Meyerhof cycle, while in the central nervous system, the energy remains virtually

unimpaired in the absence of insulin.

In diabetes mellitus the change of the metabolism of sulfhydryl compounds (glutathione, coenzyme A (CoA), mercaptoenzyme) is accompanied also by the impairment of sulfur metabolism.

The disintegration of the products of carbohydrate transformation on the level of active acetate is greatly impaired in the absence of insulin. The acetylation processes, the transformation of acetate into citrate are weakened, and the oxidation of acetate to carbon dioxide within the cycle of tricarboxylic acids is reduced.

All this is mainly the result, presumably, of insufficient formation of a reduced (SH) CoA form and leads to the weakening of the citric acid cycle. The latter is also further weakened as the result of a decrease in the formation of oxalacetic acid. As the result, further transformation of active acetate formed in the process of disintegration of fatty acids proceeds at a considerably lower rate in the citric acid cycle. The active acetate is accumulated in the liver and is transformed there into free acetoacetic acid from which beta-hydroxybutyric acid and acetone are formed.

From the free acetoacetic acid, cholesterol is synthesized comparatively easily, while only active acetate can effect the synthesis of a fatty acid. Synthesis of cholesterol is aided in a diabetic organism also by the fact that it requires a considerably smaller amount of hydrogen for hydrogenation than in the case of a fatty acid synthesis.

In diabetes mellitus the synthesis of muco- and chondro-polysaccharides is considerably reduced. This effect can be explained by the diminished resistance of the skin and connective tissue. Such a diminution in rate of synthesis depends on the reduced penetration of glucose into cells and on the lack of L-glutamine.

The decrease in glucose oxidation leads also to a slower synthesis of proteins, the latter requiring a large amount of energy.

There is a marked increase of the activity of hepatic glucose-6-phosphatase in the absence of insulin. It increases not only as the result of absence of insulin, but also under the influence of cortisone and hydrocortisone. On the other hand, under the influence of glucose-6-phosphatase glycogen synthesis diminishes, and glycogen breakdown increases, glucose is liberated from glucose-6-phosphatase, and there is increased formation of glucose from the intermediary products of carbohydrate catabolism (for example, from lactic and pyruvic acids and from glycerin). Glucose-6-phosphatase contributes to the gluconeogenesis from proteins as well as from fatty acids.

Thus, in the absence of insulin there is a decrease of the

entry of glucose into cells. There is a corresponding decrease in the formation of the energy of glucose and hydrogen oxidation needed for the hydrogenation of a number of compounds. As a result, there is a diminished formation of a reduced form of PDN (pyridinenucleotide) TPN, and glutathione, as well as a high energy phosphorus compounds. There is a marked weakening of the synthesis of glycogen, proteins, fatty acids, and muco- and chondropolysaccharides. There is an increased synthesis of cholesterol and breakdown of fatty acids, glycogen, and glucose-6-phosphatase. The formation of ketone bodies, especially from glucose, increases.

These processes explain how hyperglycemia and hyperketonemia develop when insulin is absent or insufficient.

3

Of what significance are hyperglycemia and hyperketonemia to an organism deprived of insulin? Increased concentration of sugar contributes to an increased rate of entry transition into tissues and a higher utilization. Of similar importance is the increased influx of ketone bodies into the tissues. Because of this influx, an organism deprived of insulin is able to obtain the energy essential to its existence. Hyperglycemia and hyperketonemia thus compensate to a certain degree for the reduced permeability of tissues to glucose. If the sugar content of the blood had not risen in the absence of insulin, the organism would rapidly perish from a drastic reduction of sugar in the blood and especially in the cerebral cells. Hyperglycemia and hyperketonemia, then ensure energy to the organism deprived of insulin and, thus, prolong its life.

In addition to ensuring the organism its energy, hyperglycemia also alleviates to a certain extent other impairments in a diabetic organism. It enhances formation of glycogen, fatty acids, and proteins; reduces the secretion of glucose into the blood by the liver through inhibition of gluconeogenesis; and increases the transition of blood phosphorus into the tissues. Hyperglycemia thus alleviates not only the direct effect of cessation of insulin action but some of its sequels also.

The above data enable us to understand why hyperglycemia and hyperketonemia, as well as all processes leading to their formation, had adaptative compensatory character.

In evaluation hyperglycemia and hyperketonemia as adaptive compensatory reactions, one also should not omit another facet of these reactions.

As we have seen, increased gluconeogenesis originates as the result of increased breakdown of proteins in the first place -- the more glucose formed, the higher is the disintegration of proteins of the internal organs and muscles. In realizing the very important

role of proteins in the organism and its property of using them very sparingly, developed in the process of philo- and ontogenesis, one cannot help admitting that their extensive use in the absence of insulin has an unfavorable effect -- the organism becomes weaker physically and immunobiologically. However, the intensity of protein disintegration depends not only on the degree of insulin insufficiency but also on the quantity of glucose eliminated in the urine: the more it is eliminated, the more intensive is the process of gluconeogenesis. Such dependence is particularly clear in kidney injuries leading to the reduction of glycosuria. There are diabetic patients on record who eliminated with their urine 10 to 35 g of sugar within 24 hours, despite the fact that its blood level was as high as 800-900 mg percent. These patients had no ketone bodies in their urine, and the quantity of ketone bodies in the blood was normal. These patients, with a 20-year diabetic history, suffered none of its manifestations (other than hyperglycemia and glucosuria) and felt quite comfortable. They were not even receiving insulin. One of them had a secondarily contracted kidney, and another -- glomerulosclerosis.

It follows that in diminished glucoseuria there is a drastic reduction of gluconeogenesis and a concomitant ketogenesis.

Hyperketonemia, as noted above, is also an adaptive compensatory reaction, since ketone bodies are easily oxidized in the organism and supply it with additional energy. But, in large concentration, ketone bodies exert a toxic effect on the organism, especially on the cerebral enzymes. It is precisely this effect which mainly explains the central neural origin of clinical symptoms of the precomatous state and the diabetic coma.

The enhanced cholesterol synthesis permits an increased production of glucocorticoids which cause the increase of gluconeogenesis so essential to an organism deprived of insulin. But a prolonged increase of cholesterol synthesis may contribute to the development of atheromatosis and sclerosis of the blood vessels, while an increased and prolonged secretion of adrenocortical hormones bears a definite relation to the development of intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome) and retinopathy.

The above mechanisms support the contention that, though reactions developing in the absence of insulin are truly of an adaptive compensatory character -- without them the organism would have perished much sooner -- they nevertheless carry within themselves certain dangers, especially if they develop excessively. This is the property of all adaptive compensatory reactions which develop in an impaired organism: inflammation, fever, increase of blood pressure, vomiting, etc. All of them are beneficial to a suffering organism, but only up to a certain degree of their development. Beyond this limit they themselves begin to exert a harmful effect on the organism.

While acknowledging the adaptive compensatory character of hyperglycemia and hyperketonemia in an organism deprived of insulin, one must not of course arrive at the unwise conclusion that these conditions need to be preserved. In stating the compensatory significance of hyperglycemia and hyperketonemia, we only wish to note how the organism itself has learned during the process of phylo- and ontogenesis to alleviate the damage inflicted on it through insulin deficiency. It does not mean that medicine has not found better means in this respect. Physicians possess such an arsenal of therapeutic preparations and rational measures which regulate the metabolic disturbances in diabetes mellitus considerably more effectively than do the adaptive compensatory reactions of the organism. Such therapy renders the latter superfluous.

4

As seen from the above, the concept of diabetes mellitus is much more complicated than it was 40 years ago. We cannot speak any longer of diabetes mellitus as a pancreatic disease only.

Diabetes mellitus may start with the impairment of the insular apparatus of the pancreas, but it is followed by changes in the anterior hypophyseal lobe and the adrenal glands. Diabetes mellitus may start even when the function of the insular apparatus is normal, if there is a primary enhancement of the function of the anterior hypophyseal lobe or adrenals, especially the cortical substance. Although excess of glucocorticoids increases the secretion of insulin, the compensation is not always adequate; we speak then of a "steroid diabetes." A mild diabetes mellitus of a pancreatic character becomes strongly expressed in the hyperfunction of the thyroid gland. Not infrequently diabetes mellitus emerges during the period of fading ovarian functions. It may develop or become grave (from a condition of mild or medium gravity) upon the inactivation of insulin by various proteolytic enzymes, particularly insulinase, as a result of absorption of insulin by various proteins which are detected in the blood protein fraction and under various other conditions.

Thus, while diabetes mellitus was considered before as basically a pancreatic disease it is known at the present time that this disease develops also under normal and even increased functioning of the insular pancreatic apparatus, for example, in acromegaly. In other words, while 40 years ago the consensus of opinion was that diabetes mellitus originates as the result of an absolute lack of insulin, at the present time it has become known that the condition may occur also when this hormone is relatively deficient.

Since in diabetes mellitus there is an impairment of the function of a number of endocrine glands, and an interrelationship

with the hypothalamus and the central nervous system, many authors correctly consider this disease as a disease of correlations.

A detailed analysis of functional changes in diabetes mellitus led to the isolation of processes which attest to injuries to the organism caused by the lack of insulin, and processes which characterize the fight of the organism against the injury inflicted on it. From such knowledge, the physician evaluates more correctly the significance of diabetic symptoms and is able to outline more rationally the measures needed to combat the injuries to the organism.

It is known that in steroid diabetes one strives to cause a depression of the adrenocorticotrophic function of the anterior hypophyseal lobe or the adrenals cortex, to the extent of their removal; in thyroid hyperfunction which complicates diabetes mellitus, one attempts to depress the synthesis of thyroxin, or one removes the major part of the thyroid; in diabetes mellitus appearing during the period of ovarian involution, estrogens are administered which frequently considerably alleviate the diabetic symptoms; during the development of diabetes mellitus caused by formation of antibodies to the insulin administered exogenously the attempt is made to eliminate them by means, for example, of ACTH or cortisone; insulin-resistance related to strong excitation of the sympatho-adrenal system is alleviated by pharmacological or surgical means. Thus, there are a number of therapeutic measures in existence, depending on the peculiarities of the pathogenesis of diabetes mellitus. The insufficiency of the insular apparatus itself is frequently alleviated by adjusting the patient's nutrition and manner of life, with the aid of definite doses of insulin or its substitution with other antidiabetic preparations. By using these means it is possible to eliminate the basic metabolic impairments even in the diabetes mellitus of medium or grave character. However, the insulin administration from without is to date unfortunately considerably less perfect than its entrance into the organism from the normal insular apparatus. Therefore, such residual phenomena as mild hyperglycemia and glucosuria are not infrequently encountered in the successful treatment of basic organic disturbances. It is essential to try to remove them by using only those methods which would not be harmful to the patient. It is possible to attempt their elimination by means of a more uniform apportionment of food and insulin during the day, certain reduction in the quantity of carbohydrates by substituting for them other nutritive substances (referring to patients with subnormal or normal weight), a more rational regimen, and other measures. But even with these measures it is not always possible to eliminate the residual hyperglycemia and glucosuria in all patients. Some physicians evaluate incorrectly the significance of hyperglycemia in an organism deprived of a sufficient quantity of insulin to such an extent that they resort

to extraordinary means for its elimination, such as a drastic reduction of the quantity of carbohydrates in food, thus rendering the food physiologically inadequate, or carry out a course of therapy with subshock doses of insulin. Such measures may sometimes, though quite rarely, help to eliminate, more frequently to alleviate somewhat, the residual hyperglycemia and glucosuria. These measures, however, may cause serious injury, since the patients are placed on a physiologically incorrect diet for long periods of time, while the subshock doses of insulin are far from harmless to the higher sections of the central nervous system.

In evaluating these facts on the significance of hyperglycemia, we as well as many other physicians, think (3) that since the condition cannot be eliminated by means which are harmless to the organism, as discussed above, it must be endured. Continuous and numerous observations were unable to demonstrate any harm caused by residual glucosuria and hyperglycemia to the organism of a diabetic patient who receives normal food and an adequate quantity of insulin. In attempting the elimination of residual glucosuria and hyperglycemia by all possible means, one must not forget the wise old medical rule: treatment of the patient must not cause him greater injury than the one caused by the disease itself.

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Submitted 2 July 1959

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